

## (12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization International Bureau



(43) International Publication Date  
30 September 2004 (30.09.2004)

PCT

(10) International Publication Number  
**WO 2004/083197 A3**

(51) International Patent Classification<sup>7</sup>: **C07D 307/88**

(21) International Application Number:  
**PCT/DK2004/000177**

(22) International Filing Date: 17 March 2004 (17.03.2004)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:  
60/456,415 21 March 2003 (21.03.2003) US  
PA200300440 21 March 2003 (21.03.2003) DK

(71) Applicant (for all designated States except US): **H. LUNDBECK A/S** [DK/DK]; Ottileavej 9, DK-2500 Valby-Copenhagen (DK).

(72) Inventors; and

(75) Inventors/Applicants (for US only): **PITTELKOW, Thomas**; Kalundborgvej 27, DK-4520 Svinginge (DK). **CASTELLIN, Andrea** [IT/IT]; Via Garibaldi, 15, I-35035 Mestrino (IT). **SBROGIO, Federico** [IT/IT]; Via Passo Pordoi, 9, I-30030 Favaro Veneto (IT). **DAHLBERG, Nielsen, Poul** [DK/DK]; Prejlerupvej 26, DK-4560 Vig (DK). **ZANON, Jacopo** [IT/IT]; Cannaregio, 2399, I-30100 Venezia (IT). **SØGAARD, Steen** [DK/IT]; Via Andrea Doria 2, I-35100 Padova (IT). **HUMBLE, Rikke, Eva** [DK/DK]; Æblevej 9, DK-2400 Copenhagen N (DK).

(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

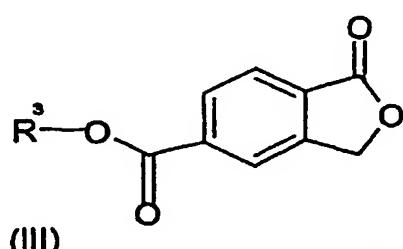
## Published:

- with international search report
- before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments

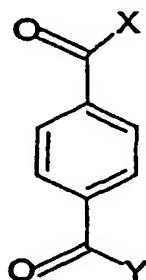
(88) Date of publication of the international search report:  
28 October 2004

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: INTERMEDIATES FOR THE PREPARATION OF CITALOPRAM AND ESCITALOPRAM



(57) Abstract: Methods for manufacture of 5-alkoxycarbonylphthalides are disclosed. The 5-alkoxycarbonylphthalides are useful in syntheses of the well-known antidepressants citalopram and escitalopram. A method for preparing an alkoxycarbonylphthalide of formula (III) comprising: (a) reacting a compound of formula (VIIIa) with a formaldehyde and oleum; and (b) addition of an alcohol R<sup>3</sup>-OH to the reaction of step (a); wherein X and Y of formula (VIIIa) may be selected independently from the group consisting of: OR<sup>1</sup>, OR<sup>2</sup>, a halogen (such as Cl, Br, I), and NR; wherein R, R<sup>1</sup> and R<sup>2</sup> are independently h or a C<sub>1-6</sub>alkyl or phenyl.



(VIIIa)

A. CLASSIFICATION OF SUBJECT MATTER  
IPC 7 C07D307/88

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, BEILSTEIN Data, CHEM ABS Data

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	EP 1 118 614 A (NORPHARMA SPA) 25 July 2001 (2001-07-25) cited in the application column 2 - column 4; examples -----	1-49
Y	WO 01/32642 A (DAHLBERG NIELSEN Poul ;PETERSEN HANS (DK); LUNDBECK & CO AS H (DK)) 10 May 2001 (2001-05-10) cited in the application page 2 -----	1-49
Y	WO 00/39112 A (DAHLBERG NIELSEN Poul ;PETERSEN HANS (DK); LUNDBECK & CO AS H (DK)) 6 July 2000 (2000-07-06) cited in the application page 5, line 26; example 1 -----	1-49
X	----- ----- ----- ----- -----	50-58

 Further documents are listed in the continuation of box C. Patent family members are listed in annex.

## \* Special categories of cited documents:

- \*A\* document defining the general state of the art which is not considered to be of particular relevance
- \*E\* earlier document but published on or after the International filing date
- \*L\* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- \*O\* document referring to an oral disclosure, use, exhibition or other means
- \*P\* document published prior to the International filing date but later than the priority date claimed

- \*T\* later document published after the International filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- \*X\* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- \*Y\* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- \*&\* document member of the same patent family

Date of the actual completion of the International search

19 July 2004

Date of mailing of the International search report

16.09.04

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2  
NL - 2280 HV Rijswijk  
Tel: (+31-70) 340-2040, Tx. 31 651 epo nl,  
Fax: (+31-70) 340-3016

Authorized officer

Fazzi, R

## INTERNATIONAL SEARCH REPORT

Ir Application No  
PCT/DK2004/000177

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 98/19513 A (PETERSEN HANS ;LUNDBECK & CO AS H (DK)) 14 May 1998 (1998-05-14) cited in the application page 7; examples 1,2 -----	1-49
X	ANZALONE ET AL.: "Substituent Effects on Hydrogenation of Aromatic Rings: Hydrogenation vs. Hydrogenolysis in Cyclic Analogues of Benzyl Ethers" J. ORG. CHEM., vol. 50, 1985, pages 2128-2133, XP002282189 cited in the application page 2129; example 22 -----	50-58
X	SUGIMORI, AKIRA ET AL: "Radiation-induced reduction of aromatic carboxylic esters in alcoholic solutions" CHEMISTRY LETTERS (1980), (5), 483-6, 1980, XP001189503 cited in the application page 484; example 6 -----	50-58
X	LEROY S FORNEY: "REACTION OF TEREPHTHALIC ACID WITH FORMALDEHYDE IN SULFUR TRIOXIDE MEDIA" JOURNAL OF ORGANIC CHEMISTRY, AMERICAN CHEMICAL SOCIETY. EASTON, US, vol. 35, no. 5, May 1970 (1970-05), pages 1695-1696, XP002936415 ISSN: 0022-3263 cited in the application page 1696 -----	50-58

# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/DK2004/000177

## Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1.  Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:
  
2.  Claims Nos.: because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
  
3.  Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this International application, as follows:

see additional sheet

1.  As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
  
2.  As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
  
3.  As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
  
4.  No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

The additional search fees were accompanied by the applicant's protest.  
 No protest accompanied the payment of additional search fees.

**FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210**

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

**1. claims: 1-49**

Claim 1 and dependent upon relate to a method for preparing an alkoxy carbonyl phthalide of formula (III), comprising reacting a compound of formula (VIIIa) with a formaldehyde and oleum and then adding an alcohol of formula R3OH.

**2. claims: 50-56**

Claim 50 and dependent upon disclose a method for preparing an intermediate suitable for the synthesis of citalopram or escitalopram, comprising the steps of preparing a compound of formula (III) and then isolating it.

**3. claims: 57-58**

Claims 57 and 58 relate to compounds of formula (III).

**INTERNATIONAL SEARCH REPORT**

Information on patent family members

International application No

PCT/DK2004/000177

Patent document cited in search report	Publication date	Patent family member(s)			Publication date
EP 1118614	A 25-07-2001	IT MI20000050 A1	18-07-2001	US 6458973 B1	01-10-2002
		AT 219489 T	15-07-2002	AU 2679801 A	31-07-2001
		BG 106925 A	30-01-2004	BR 0107853 A	29-10-2002
		CA 2397497 A1	26-07-2001	CN 1406236 T	26-03-2003
		DE 60000226 D1	25-07-2002	DE 60000226 T2	06-03-2003
		DK 1118614 T3	14-10-2002	WO 0153284 A1	26-07-2001
		EP 1118614 A2	25-07-2001	EP 1187822 A1	20-03-2002
		ES 2178626 T3	01-01-2003	HK 1042290 A1	18-07-2003
		HU 0204187 A2	28-03-2003	JP 2001206881 A	31-07-2001
		PT 1118614 T	29-11-2002	US 2003009038 A1	09-01-2003
		ZA 200205475 A	10-10-2003		
WO 0132642	A 10-05-2001	AU 7902400 A	14-05-2001	BR 0015471 A	09-07-2002
		CA 2389379 A1	10-05-2001	CN 1391567 T	15-01-2003
		WO 0132642 A1	10-05-2001	EP 1235819 A1	04-09-2002
		HR 20020405 A2	29-02-2004	IT MI20002342 A1	29-04-2002
		JP 2003513084 T	08-04-2003	US 2002165403 A1	07-11-2002
		US 6403813 B1	11-06-2002		
WO 0039112	A 06-07-2000	AT 236145 T	15-04-2003	AU 764161 B2	14-08-2003
		AU 1774200 A	31-07-2000	BR 9916955 A	11-09-2001
		CA 2356188 A1	06-07-2000	CN 1331686 T	16-01-2002
		CZ 20012335 A3	12-12-2001	DE 69906580 D1	08-05-2003
		DE 69906580 T2	12-02-2004	DE 69906580 T2	12-02-2004
		WO 0039112 A1	06-07-2000	WO 0039112 A1	06-07-2000
		DK 1140886 T3	28-07-2003	DK 1140886 T3	28-07-2003
		EA 3057 B1	26-12-2002	EA 3057 B1	26-12-2002
		EP 1140886 A1	10-10-2001	EP 1140886 A1	10-10-2001
		ES 2195644 T3	01-12-2003	ES 2195644 T3	01-12-2003
		HU 0104856 A2	29-04-2002	HU 0104856 A2	29-04-2002
		IT MI992696 A1	25-06-2001	IT MI992696 A1	25-06-2001
		JP 2002533450 T	08-10-2002	JP 2002533450 T	08-10-2002
		NO 20013150 A	20-08-2001	NO 20013150 A	20-08-2001
		NZ 512073 A	31-10-2003	NZ 512073 A	31-10-2003
		PL 348608 A1	03-06-2002	PL 348608 A1	03-06-2002
		PT 1140886 T	29-08-2003	PT 1140886 T	29-08-2003
		SI 1140886 T1	31-08-2003	SI 1140886 T1	31-08-2003
		SK 8962001 A3	04-03-2003	SK 8962001 A3	04-03-2003
		TR 200101796 T2	21-11-2001	TR 200101796 T2	21-11-2001

**INTERNATIONAL SEARCH REPORT**

Information on patent family members

II. International application No

PCT/DK2004/000177

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
WO 0039112	A	US	2002019546 A1	14-02-2002
		ZA	200104262 A	11-12-2001
WO 9819513	A 14-05-1998	AT	205824 T	15-10-2001
		AU	737610 B2	23-08-2001
		AU	6609898 A	29-05-1998
		BG	104116 A	29-12-2000
		BR	9810499 A	13-03-2001
		CA	2291067 A1	14-05-1998
		CN	1138768 C	18-02-2004
		CZ	20000062 A3	12-07-2000
		DE	69801764 D1	25-10-2001
		DE	69801764 T2	04-07-2002
		DE	1015416 T1	05-10-2000
		WO	9819513 A2	14-05-1998
		DK	1015416 T3	05-11-2001
		EA	1728 B1	27-08-2001
		EP	1015416 A2	05-07-2000
		ES	2148120 T1	16-10-2000
		HU	0003177 A2	28-04-2001
		JP	3526581 B2	17-05-2004
		JP	2002509526 T	26-03-2002
		NO	20000008 A	03-01-2000
		NZ	501737 A	26-10-2001
		PL	338015 A1	25-09-2000
		PT	1015416 T	28-03-2002
		SI	1015416 T1	31-12-2001
		SK	32000 A3	11-07-2000
		TR	200000066 T2	21-11-2000
		US	6229026 B1	08-05-2001
		ZA	9805981 A	28-01-1999